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NOVARTIS VACCINES AND DIAGNOSTICS INC.
INTELLECTUAL PROPERTY R338
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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Response to Arguments

Prior Art Rejections maintained

1. Applicants argue that Domenighini fails to describe an LT-A having both the amino acid positions corresponding to Ser-63 and Arg-192 replaced with another amino acid. This has been fully and carefully considered but is not deemed persuasive. As stated in the body of the rejection above, Domenighini et al does teach double mutants and much more. Claim 1 of Dominighini specifically recites that position Ser-63 of CT-A or LT-A may be replaced with another amino acid ***and*** claim 2 specifically recites at least one additional amino acid specifically including Arg-192 may also be replaced with another amino acid, e.g., the same double mutant is included in the scope of the teachings of Domenighini et al. The claims of Dominighini, as well as the teachings of their specification, clearly anticipate the claimed invention.

Applicants argue that Domenighini fails to describe an LT-A having both the amino acid positions corresponding to Ser-63 and Arg-192 replaced with another amino acid. This has been fully and carefully considered but is not deemed persuasive. As stated in the body of the rejection above, Domenighini et al does teach double mutants and much more. Claim 1 of Dominighini specifically recites that position Ser-63 of CT-A or LT-A may be replaced with another amino acid ***and*** claim 2 specifically recites at least one additional amino acid specifically including Arg-192 may also be replaced with another amino acid, e.g., the same double mutant is included in the scope of the teachings of Domenighini et al. Clements et al show DNA that encodes a mutant detoxified heat labile toxin of E.coli and mutant detoxified cholera toxin, wherein the

mutation at position 192 is mutation from Arg-192 to Gly-192 in an analogous art for the purpose of obtaining a detoxified protein that still evidences adjuvant activity for induction of an enhanced immune response. It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to modify the mutation of Domenighini at position 192 from Asn to Gly as taught by Clements, because Clements and Domenighini et al are both directed to the site directed mutagenesis of heat labile toxin of E.coli at position 192, and Clements et al teaches the advantage of substituting Gly at position 192 as yielding a stable, detoxified, mutant that is devoid of ADP-ribosyl transferase activity, but retains its activity as an immunological adjuvant (see Clements, col. 8, lines 24-27 and 28-50). The person of ordinary skill in the art would have been motivated to substitute the amino acid for Gly at position 192, because the resultant protein/polypeptide would lack the potential to become toxic due to proteolytic activation, resulting in "no real or potential side-effects, such as diarrhea, associated with its use (see col. 10, lines 5-14). In the absence of a showing of unexpected results, Domenighini et al in view of Clements et al obviate the instantly claimed invention.

Applicants further argue that this substitution has no be shown by Clements and Domenighini to not only retain immunogenicity, but also to result in the protein being detoxified and more resistant to trypsin proteolysis than wild-type CT-A or LT-A. The references (Domenighini and Clements) teach the identical mutations. Clements et al does teach the advantage of substituting Gly at position 192 as yielding a stable,

detoxified, mutant that is devoid of ADP-ribosyl transferase activity, but ***retains its activity*** as an immunological adjuvant (see Clements, col. 8, lines 24-27 and 28-50). Additionally, the proteins would inherently possess the property of being more resistant to trypsin proteolysis. The person of ordinary skill in the art would have been motivated to substitute the amino acid for Gly at position 192, because the resultant protein/polypeptide would lack the potential to become toxic due to proteolytic activation, resulting in "no real or potential side-effects, such as diarrhea, associated with its use (see col. 10, lines 5-14). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Enablement Rejection:

2. Applicants argue that since the trypsin cleavage site of LT was well-known at the time of filing, it would be reasonable to expect that the properties of the exemplified Arg192 mutants are shared by other mutants which remove the trypsin recognition sequence. Park et al has been cited to show that the properties of mutations to Ser63 other than those exemplified can be extrapolated to a certain degree. These arguments have been fully and carefully considered but are not deemed persuasive. Applicants have not shown the particular substitution and the result it produces, with the exception of Arg-192 to Asn or Gly. Applicants have provided no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of

different amino substitutions and the nature and extent of the changes that can be made. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

3. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 7:30 AM-6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645